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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,126	06/22/2001	Jennifer L. Schmitke	2685.2030-000	9053

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EXAMINER
HAGHIGHATIAN, MINA

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 03/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/888,126	Applicant(s) SCHMITKE ET AL.	
	Examiner Mina Haghighatian	Art Unit 1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-60 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-60 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, 22, 23, 42 and 43 recite the limitation "per receptacle" in the independent claims. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edwards et al (5,985,309).

Edwards teaches particle incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system, methods of preparation and administration. Exemplary surfactants include dipalmitoylphosphatidylcholine (DPPC). Exemplary hydrophilic or hydrophobic complexes include insulin and protamine. The particles are aerodynamically light particles with a tap density of less than 0.4 g/cm^3, a mean diameter between 5 and 30 micron and an aerodynamic diameter between 1 and 5 microns (col. 3, line 56 to col. 4, line 17).

Edwards discloses that administration of the particles to the lung by aerosolization permits deep lung delivery of relatively large diameter therapeutic aerosols, for example greater than 5 micron in mean diameter. The particles can be fabricated with features which enhance aerosolization via dry powder inhaler devices, and lead to lower deposition in the mouth, throat and inhaler device (col. 5, lines 29-47).

Edwards also discloses that in addition to the therapeutic agents, the formulations may and preferably do include one or more excipients such as sugars, proteins and surfactant (col. 6, line 65 to col. 7, line 2). Targeting molecules can be attached to the particles via reactive functional groups on the particles. For example, targeting molecules can be attached to the amino acid groups of functionalized polyester graft copolymer particles such as poly(lactic acid-co-lysine) (col. 11, lines 48-60). Therapeutic agents suitable for such preparation include insulin (col. 12, lines 16-47).

Edwards discloses examples of particles such as insulin:albumin:lactose:DPPC in example 9. The particles are said to comprise 60% DPPC, 2% insulin, 19% albumin and 19% lactose. Two solutions are made of the ingredients, then they are combined and spray dried to produce particles. Example 11 discloses preparation method of sustained release insulin particles and example 12 discloses preparation of insulin:protamin:zinc complexes.

Edwrads lacks specific disclosure of sodium citrate in the preparations, however it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have substituted lactose with sodium citrate because lactose is not a recommended carrier/excipient for anti-diabetic preparations since it may increase patient's serum sugar level. Furthermore, Edwards does not disclose various concentration ranges for DPPC, however it would have been obvious to one of ordinary skill in the art to modify the amount of carrier based on the amount of active ingredient

needed. Also it is noted that generally, optimization of ranges will not support patentability.

Claims 1-2, 12-15, 18-20, 30-36, 39-40, 50-56 and 59-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohane et al (2002/0150626 A1).

Kohane teaches lipid-protein-sugar particles for delivery of nucleic acids. The polynucleotide may be modified by chemical or biological means. In certain preferred embodiments, these modifications lead to increased stability of the polynucleotide. The polynucleotide encodes a protein or peptide such as insulin. The protein component of the matrix may range from 0 to 99%, more preferably 1 to 80% and most preferably 1 to 60% (see [0034], [0037] and [0048]).

Kohane discloses that the lipid portion of the matrix may range from 0 to 99%, more preferably from 3 to 99%. Any lipid known in the art is suitable for use in the said preparation which includes DPPC ([0045] and [0046]). The sugar component of the formulation may range from 0.5 to 40% ([0053]).

Kohane also discloses that the formulations may be in the form of oral, intranasal, bucal, etc ([0060]). The powder form of the preparation may include excipient or carrier such as sodium citrate ([0065]). The method of preparation of the formulation include spray drying the solutions to make particles for inhalation ([0090], [0115] and page 11/11). Table 1 shows various concentration ranges for DPPC and the median diameter in the lipid-protein-sugar particles. Typical diameters were in the range of 3 to 5 microns.

Kohane does not exemplify a composition containing DPPC, insulin and sodium state, however it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified Kohane's teachings on lipid-protein-sugar particles by substituting sodium citrate for sugar, because anti-diabetic preparations can be more suitable for patients without addition of sugar, and also because sodium citrate is taught by Kohane as a suitable excipient for powder formulations.

Claims 1-9, 12-27, 30-47 and 50-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patton et al (5,997,848) in view of Betbeder et al (6,017,513).

Patton teaches that systemic delivery of insulin to a mammalian host is accomplished by inhalation of a dry powder of insulin, which is rapidly absorbed through the alveolar regions of the lung. Insulin dry powders are prepared by dissolving insulin in an aqueous buffer to form a solution and spray drying the solution to produce substantially amorphous particles having a particle size less than 10 micron, preferably less than in the range of 0.1 to 5 micron. Optionally the pharmaceutical carrier is also dissolved in the buffer, to form a homogenous solution, wherein spray drying of the solution produces individual particles comprising insulin, carrier buffer and any other compounds which were present in the solution. The carrier is preferably an amino acid, such as glycine, lysine, etc (col. 3, lines 9-21; 53-68 and col. 4, lines 43-60).

Patton discloses that insulin dry powders suitable for use in the present invention include amorphous insulin, crystalline insulin or mixtures thereof. The preferred method of forming insulin powders comprising particulates in the desired size range is spray

drying, where pure bulk insulin is first dissolved in a physiologically acceptable aqueous buffer, typically a citrate buffer such as sodium citrate (col. 6, lines 11-16 and 43-60). The preferable concentration ranges for insulin is 5 to 95% and for the carrier material is 5 to 95%. The presence of carrier material in the particles which are delivered to the alveolar region of the lung has been found not to significantly interfere with systemic absorption of insulin (col. 7, lines 1-27).

Patton also discloses that the individual dosages on a per inhalation basis, typically being in the range from 0.5 mg to 10 mg, and the total dosage during a single respiratory administration is in the range of 0.5 to 15 mg (col. 8, lines 25-32). Patton lacks teachings on using DPPC.

Betbeder et al teach a method for the mucosal administration of a substance to a mammal. Pharmaceutical substances may be administered either in the absence or in the presence of a carrier. Various purposes may be served by such carriers, such as the controlled release of biologically active molecules, and the targeting of biologically active molecules to specific tissues (col. 1, lines 50-55). Liposomes are often used as carriers for substances. They have shown potential a controlled release drug delivery system and as immunological adjuvants (col. 2, lines 3-6). A preferred phospholipid is dipalmitoylphospatidylcholin (DPPC) (col. 7, lines 13-14). Additional compounds may be added to the phospholipids such as surfactant agents and lipoproteins (col. 7, lines 26-31).

Betbeder discloses that the therapeutic agent may be any composition of matter used in the treatment of disease and conditions that afflict mammals, such as anti-diabetics agents (col. 8, lines 16-28). Biovectors are particularly effective in delivering biological molecules to the mucosa for the purposes of this specification, a biological molecule is polymer of a type that occurs in nature, or a monomer or moiety thereof. Such polymers typically comprise monomers such as amino acids (col. 9, lines 31-43).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have combined the teachings of Patton on dry powder particles of insulin and sodium citrate for inhalation to alveolar region of the lung, with the teachings of Betbeder on using DPPC as a suitable carrier for therapeutic agents, with the reasonable expectations of producing more stable and more potent insulin powders for administration through pulmonary system for systemic absorption.

Double Patenting

Claims 1-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/ 179,463. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claims of the copending application No. 10/179,463 are within the scope of the claims of the instant application. In particular, for example in claim 1, "60% DPPC" is within the range of "approximately 60% DPPC". Also in dependent claims the variation of concentration

ranges for DPPC is an optimization of ranges and would vary according to the amount of active agent desired for the preparation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 703-308-6330. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jose Dees can be reached on 703-308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

Mina Haghighatian
March 6, 2003

MICHAEL G. HARTLEY
PRIMARY EXAMINER